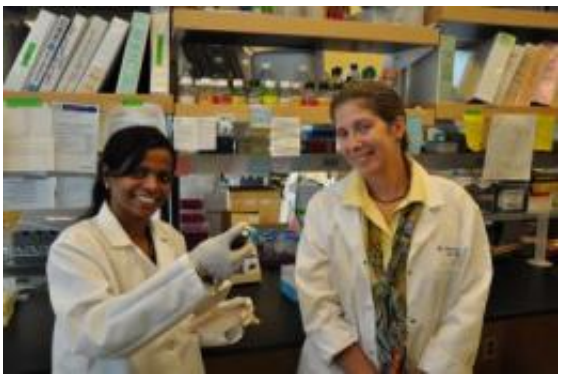
Cell biologists describes mechanism by which some people may be more susceptible to colon cancer

February 9 2012



Karthikeyani Chellappa (left) is a postdoctoral researcher in the lab of Frances Sladek, a professor of cell biology and toxicologist at UC Riverside. Credit: Photo credit: UCR Strategic Communications.

An international research team led by cell biologists at the University of California, Riverside has uncovered a new insight into colon cancer, the third leading cause of cancer-related deaths in the United States. The research provides potential new avenues for diagnosing and treating the disease.

Led by Frances Sladek at UC Riverside and Graham Robertson at the University of Sydney, Australia, the team analyzed about 450 human colon cancer specimens and found that in nearly 80 percent of them the

variants of a gene, *HNF4A*, are out of balance.

Human beings express several variants of the *HNF4A* gene, classified as P1 and P2 variants. Some tissues, like liver, have just one type of variant but the colon has both P1 and P2 variants. The P1 variant is found in the nuclei of cells in the normal colon but in the human colon cancer samples this variant is frequently either absent or located outside of the nucleus and, presumably, no longer functional.

Using human colon cancer cell lines and *in vitro* assays, the researchers found that the imbalance observed in the human tumor tissues seemed to be the result of a complex, multi-step process by an enzyme, Src kinase. Src kinase has been known to be activated in colon cancer but, until now, it was not known to act on the HNF4a protein (*HNF4A* is the gene, a stretch of DNA; HNF4a is the protein encoded by *HNF4A*). The UCR group found that activated Src modifies the P1 but not the P2 variant. The net result is loss of the P1 variant in the nuclei of cells in the colon.

Study results appeared online last week in the Proceedings of the National Academy of Sciences.

"Loss of nuclear P1 HNF4a protein in the colon may be an early sign of colon cancer," explained Sladek, a professor of cell biology and toxicologist. "A healthy colon has a good but delicate balance of the two HNF4a variants. If you could prevent the loss of the P1 variant via drugs, you might be able to maintain a normal colon and prevent colon cancer."

The researchers found another factor that increases a person's susceptibility to the disease: certain "single nucleotide polymorphisms" or SNPs located in the *HNF4A* gene. An SNP is a DNA sequence variation - a minor change in the genomic sequence that accounts for the variations we see between individuals. SNPs are the most common type

of genetic variation among people.

"Individuals with certain SNPs may be more susceptible to colon cancer," said Karthikeyani Chellappa, a postdoctoral researcher in Sladek's lab and the first author of the research paper. "That's because these SNPs result in a greater amount of modification and a faster degradation of HNF4a by Src, at least in cell-based assays. It still needs to be investigated, though, whether individuals carrying these SNPs are indeed more susceptible to colon cancer."

Sladek noted that drugs are already available for inhibiting the activity of Src kinase.

"Some of these drugs are in clinical trials for colon cancer," she said. "It would be exciting to determine whether these drugs can maintain the P1 HNF4a protein levels, as well as inhibit the Src kinase activity."

A multifactorial disease influenced by genetics and the environment, colon cancer starts as a small polyp in the large intestine (colon) or the rectum (end of the colon). While most of the polyps are benign, some do turn cancerous. With proper screening, the disease can be detected early, when it is most curable.

Provided by University of California - Riverside